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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,517	03/16/2004	Xiaoyang Qi	0010872.0556916	4062

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FROST BROWN TODD, LLC
2200 PNC CENTER
201 E. FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
SANG, HONG	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@fbtlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/801,517	QI, XIAOYANG	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *9-49 and 58-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

RE: Qi

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2008 has been entered.

2. Claims 1-65 are pending. Claims 9-43, 58 and 64 have been withdrawn from consideration as being drawn to non-elected inventions. Claims 1, 2, 5, 7, 8, and 50-57 have been amended. Claims 44-49, 59-63 and 65 have been withdrawn by applicants.

3. Claims 1-8, and 50-57 are under examination. Due to restriction and species election, claims are examined to the extent that the structure analog of phosphatidylserine is dioleoylphosphatidylserine (DOPS).

Objections withdrawn

4. The objection to claims 44-49, 59-63, and 65 because the claims depend from a non-elected invention is withdrawn in view of applicant's withdrawn of the claims from further consideration (see response page 18, lines 1-3).

Rejections Withdrawn

5. The rejection of claim 7 under 35 U.S.C. 112, second paragraph for lacking antecedent basis is withdrawn in view of applicant's amendment to the claim.

6. The rejection of claims 50-57 under 35 U.S.C. 112, first paragraph, because the phrase "are contacted with an acidic buffer" is considered new matter is withdrawn in view of applicant's amendment to the claims.

7. The rejection of claims 1-8, 44-49, 63, and 65 under 35 U.S.C. 112, first paragraph because the phrases "wherein the nanovesicle has an average diameter in the range of 10-800 nm" recited in claim 1, "wherein the nanovesicle has a diameter in the range 0.01 to 1 μm" recited in claim 63, and "wherein the nanovesicle formed has a diameter in the range 10-800 nm and exhibits anti-tumor activity" recited in claims 44-49 and 65 (limitation from claim 64) are considered new matter is withdrawn in view of applicant's amendment to the claims.

8. The rejection of claims 1-8, 44-57, and new claims 59-63 and 65 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'brien et al. (WO9503821A1), as evidenced by Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS) is withdrawn in view of the Declaration of Qi. The Declaration states that the lipid/saposin vesicles formed by Vaccaro's method do not have anti-tumor activity (see the Declaration, paragraph 3), and each working example described in the instant specification builds upon the earlier one(s), incorporating all of

the same information regarding materials and methods (see the Declaration, page 4). The Declaration states that the claimed anti-tumor composition comprises a saposin-C-DOPS nanovesicle complex not a mixture of nanovesicles and saposin-C suspended in a carrier (see paragraph 5).

9. The rejection of claims 1-8, 44-57, and new claims 59-63 and 65 under 35 U.S.C. 103(a) as being unpatentable over Vaccaro et al. (FEBS 1993, 336(1): 159-162) in view of the teachings of O'brien et al. (WO9503821A1), Vaccaro et al. (FEBS, 1994, 349: 181-186, IDS), and Egas et al. (J. Biol. Chem. 2000, 275(49): 38190-38196) is withdrawn in view of the Declaration of Qi. The Declaration states that the lipid/saposin vesicles formed by Vaccaro's method do not have anti-tumor activity (see the Declaration, paragraph 3), and each working described in the instant specification example builds upon the earlier one(s), incorporating all of the same information regarding materials and methods (see the Declaration, page 4). The Declaration states that the claimed anti-tumor composition comprises a saposin-C-DOPS nanovesicle complex not a mixture of nanovesicles and saposin-C suspended in a carrier (see paragraph 5).

10. The provisional rejection of claims 1-3, 44-47, 50-52 and new claims 59-61 and 65 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16, 17, 21 and 22 of copending Application No. 10/967,921 in

view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is withdrawn in view of applicant's abandonment of the copending Application No. 10/967,921.

Rejections Maintained

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

11. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

The response states that the attached references J. Biol. Chem., Vol. 271, No. 12, pp. 6874-6880, 1996, and J. Biol. Chem., Vol. 276, No. 29, pp. 27010-27017, 2001, show that the structure of the Saposin C molecule has 5 helices, which was well-defined at the time the present application was filed, and the specification identifies that the domains responsible for activity, i.e., a plasma membrane binding domain, is made up of the H-1 and H-5 helices in SEQ ID NO: 2. With the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences that encode a polypeptide with at least 95% sequence identity with SEQ ID NO: 2. Further, the art-recognizes the correlation between the H-1 and H-5 helical structure of SEQ ID NO: 2 and novel activity. The amino acid substitutions outside of the two identified functional domains are unlikely to greatly affect activity. Thus, a correlation exists between the function of the claimed protein and the structure of the disclosed binding and catalytic domains. As described in the attached declaration of Qi, the helix structures are well described: the H-1 and H-5 helices then provide for the ability of the polypeptide to embed within the phospholipid layer of the nanovesicle, providing the biological activity as shown.

Applicant's arguments and the Declaration of Qi under 37 CFR 1.132 have been carefully considered but are not persuasive. The amendment to the claims does not overcome the rejection for the following reasons. The claims have been amended to recite a core structure for the claimed genus, i.e. "wherein the polypeptide comprises H1 through H5 helix regions of saposin C and retains plasma membrane affinity" (see claim 1), or "wherein the polypeptide includes sequences which form helix regions H1 and H5 of saposin C, which embed within the lipid bilayer of the nanovesicle" (see claim 50). While the prior art and the Declaration of Qi show that the H1 and H5 helix regions are required for the function of retaining plasma membrane affinity, the claimed function is not retaining plasma membrane affinity, but an anti-tumor activity. The specification does not establish a correlation between plasma membrane affinity and anti-tumor activity. The specification defines the "plasma membrane affinity" refers to an ability to interact with phospholipid surfaces through electrostatic or hydrophobic interactions (emphasis added, see the instant specification, page 9, lines 1-2). However, the specification has not shown that the plasma membrane affinity is the sole factor for the anti-tumor activity. Although with the aid of a computer, one of skill in the art could identify all of the nucleic acid sequences that encode a polypeptide with at least 95% sequence identity with SEQ ID NO: 2, the level of skill and knowledge in the art is such that one of ordinary skill in the art would not be able to identify without further testing which of those proteins having at least 95% identity to SEQ ID NO: 2 (if any) have the anti-tumor activity. The phrase "one or more conservative substitution" encompasses one amino acid up to as many as all amino acid substitutions outside the H1 and H5

helix regions of the SEQ ID NO: 2. The specification does not show that the regions outside the H1 and H5 helix are not required for performing anti-tumor activity. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the applicant was in possession of the claimed genus of proteins based on disclosure of the single species of SEQ ID NO: 2. See the Written Description Training Materials, Revision 1, March 25, 2008, Example 10 (Product claimed by its function). For the forgoing reasons, the rejection is maintained.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

12. The rejection of claims 1-8, and 50-57 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide of SEQ ID NO.2, does not reasonably provide enablement for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2, or a polypeptide of SEQ ID NO:2 having one or more conservative substitutions is maintained.

The response states that applicants have amended the claims to remove reference to an agent comprising any and all inner leaflet component, and any and all prosaposin-related polypeptide of an amino acid sequence that is at least 80% identical.

The amendment to the claims does not overcome the rejection. The claimed polypeptide encompasses a genus of molecules that are at least 95% identical to SEQ ID NO:2, or having one or more conservative substitutions in the SEQ ID NO:2. The claims have been amended to recite a core structure for the claimed genus, i.e. "wherein the polypeptide comprises H1 through H5 helix regions of saposin C and retains plasma membrane affinity" (see claim 1), or "wherein the polypeptide includes sequences which form helix regions H1 and H5 of saposin C, which embed within the lipid bilayer of the nanovesicle" (see claim 50). While the prior art and the Declaration of Qi show that the H1 and H5 helix regions are required for the function of retaining plasma membrane affinity, the claimed function is not retaining plasma membrane affinity, but an anti-tumor activity. The specification does not establish a correlation between plasma membrane affinity and anti-tumor activity. The specification defines the "plasma membrane affinity" refers to an ability to interact with phospholipid surfaces through electrostatic or hydrophobic interactions (emphasis added, see the instant specification, page 9, lines 1-2). However, the specification has not shown that the plasma membrane affinity is the sole factor for the anti-tumor activity. Because the structure that is required for performing the anti-tumor activity is unknown, given the unpredictability of the protein chemistry, and the large number of polypeptides claimed, combined with the lack of working examples showing the claimed variants have anti-tumor actively, it would require undue experimentation to perform the invention as broadly claimed.

Double Patenting

13. The rejection of claims 1-3, and 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

The response states a Terminal Disclaimer will be filed if conflicting claims are issued.

Since no Terminal Disclaimer has been filed, the rejection is maintained.

New Grounds of Objections and Rejections

Claim Objections

14. Claims 1-8 are objected to because of the following informalities: claim 1 recites "wherein the phospholipid forms a nanovesicle having the polypeptide embedded within its polypeptide embedded nanovesicle". The meaning of the phrase "the polypeptide embedded within its polypeptide embedded nanovesicle" (emphasis added) is unclear. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-8 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

The phrases "wherein the polypeptide comprises H1 through H5 helix regions of saposin C and retains plasma membrane affinity" recited in claim 1, and "wherein the polypeptide includes sequences which form helix regions H1 and H5 of saposin C, which embed within the lipid bilayer of the nanovesicle" recited in claim 50 are considered new matter since the specification, drawings and claims as filed do not provide clear support for such limitations. In the introduction of the background of the invention, the specification discloses that saposins associate with lipid membranes by embedding into the outer leaflets, and the H-1 and H-5 helices are integral to this process, suggesting that proper membrane interaction of saposin C affects its specificity and activity (see the specification, paragraph [0007]). There is no support for "a polypeptide comprises H1 through H5 helix regions of saposin C" (emphasis added). There is no support for the claimed saposin C-associated polypeptide/phospholipid nanovesicles comprising the polypeptide comprising H1 through H5 helix regions of saposin C, or sequences which form helix regions H1 and H5 of saposin C.

If applicant believes that support for the above-mentioned phrases or terms is present in the specification, claims or drawing as originally filed, applicant must, in responding to this action, point out with particularity, where such support may be found.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-8 and 50-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Brien (US 5,700,909, Date of Patent: 12/23/1997), in view of Liu et al. (WO 98/33482, Pub. date: 8/6/1998), and Habberfield (US 2002/0099001A1, Pub Date: 7/25/2002, earlier effective filing date 2/1/1995).

O'Brien teaches a method of treatment of demyelination disorders in mammal comprising administering to the mammal a pharmaceutically effective amount of saposin C, wherein the saposin C may be advantageously enclosed in a liposome-like (lamellar) structure (see column 4, lines 48-63, and column 9, lines 52-59). O'Brien discloses that the liposome encapsulation technology is well known (see column 9, lines 52-59). O'Brien discloses the amino acid sequence of Saposin C (SEQ ID NO:4) (see column 7, lines 4-5), which is 100% identical to the instant SEQ ID NO:2 (see sequence alignment, Exhibit A).

O'Brien does not teach that the liposome is made of phosphatidylserine, dioleoylphosphatidylserine (DOPS), or phosphatidylethanolamine. O'Brien does not

disclose the recited molar ratio and mass ratio of saposin C to phospholipid. However, these deficiencies are made up for in the teachings of Liu and Habberfield.

Liu et al. teach encapsulation of a drug in liposome vesicle for in vivo drug delivery, wherein the liposome vesicle is a single bilayer or multiple bilayers vesicles consisting of phospholipids in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecules, wherein the lipid is preferably phosphatidylcholine (PC), phosphatidylethanolamine (PE), or phosphatidylserine (PS) (see page 2, lines 28-30, page 3, lines 10-11), and the molar ratio of the drug molecules to the lipid is 1:2 to 1:20 or 1:2 to 1:100 (see page 3, lines 14-22). It is noted that according to the drug/lipid ratio of 1:2 to 1:100, the calculated mass ratio of the saposin C to the phosphatidylserine is 5:1-1:9. Liu et al. teach that the size of the liposome can vary from about 10nm to about 25 μm, (see page 6, lines 1-6, and claims).

Habberfield teaches liposomes composed of DOPS for drug delivery (see paragraph 0027).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the liposome composed of phosphatidylserine such as DOPS or phosphatidylethanolamine to encapsulate saposin C with the molar ratio taught by Liu for the treatment of demyelination disorders in view of the teachings of Liu and Habberfield. One of ordinary skill in the art would have been motivated to do so because phosphatidylserine such as DOPS and phosphatidylethanolamine were wildly used for make drug delivery liposomes as shown by the teachings of Liu and Habberfield. One of ordinary skill in the art would have a reasonable expectation of

success to use the liposome composed of phosphatidylserine such as DOPS or phosphatidylethanolamine to encapsulate saposin C with the molar ratio taught by Liu for the treatment of demyelination disorders because using various lipids including phosphatidylserine such as DOPS or phosphatidylethanolamine for making drug delivery liposomes were conventional at the time the invention was made.

Although the cited references do not teach that the saposin/liposome nanovesicles comprising saposin C, and phosphatidylserine such as dioleoylphosphatidylserine or phosphatidylethanolamine have anti-tumor activity or promote death in cancer cells, the claims are drawn to a product *per se* and inherently, such nanovesicles would have anti-tumor activity. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643
12/12/08

/Christopher H Yaen/
Primary Examiner, Art Unit 1643